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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/332,063	06/14/1999	LARS HOLMGREN	3362-0101P	2465

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 06/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/332,063	HOLMGREN ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,26-33 and 35-50* is/are pending in the application.

4a) Of the above claim(s) *26-29,36,37 and 39-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,30-33,35,38,49 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Please note that the examiner assigned to this application has changed.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 26, 2004 has been entered.

Claims 1, 3 and 6 have been amended. Claims 2, 8-25 and 34 have been canceled. Claims 39-50 have been added. Claims 26-29, 36 and 37, remain withdrawn from consideration. New claims 39-49, also drawn to non-elected inventions, are withdrawn from consideration. It is noted that applicant has amended withdrawn claims 26-28, 36 and 37. Claims 1, 3-7, 30-33, 35, 38, 49 and 50 are under consideration.

Sections of Title 35, US Code not found in this action can be found in a previous action.

Acknowledgement is made of applicants claims to an earlier effective filing date via the provisional applications of 60/089,266 and 60/114,386. Upon review of both provisional applications, it is noted that only the '386 application provides support for the instant claimed variants, therefore the instant application will be given an effective priority date of Dec 29, 1998 consistent with the '386 application.

Claims 3-5, 30-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites "said sequence has 80% sequence homology or greater to SEQ ID NO:4 and has sequence homology equal to or greater than 80% to SEQ ID NO:2.... It is unclear how claim 3 further limits claim 1 because the limitation of having 80% sequence homology to SEQ ID NO:4 is already present in claim 1, and further SEQ ID NO:4 is a subfragment of SEQ ID NO:2 from residue 462 to residue 604, thus the recitation of having "sequence homology equal

to or greater than 80% to SEQ ID NO:2" does not require the recitation of having "80% sequence homology or greater to SEQ ID NO:4" because SEQ ID NO:4 is subfragment of SEQ ID NO:2. It is also noted that SEQ ID NO:3 is a consensus sequence incorporating variant residues at positions 135 and 148-150. Claim 1 has been amended to specify a mammalian protein rather than a human protein. The specification identifies SEQ ID NO:4 as a human protein. It is unclear if applicants intent was to claim SEQ ID NO:3 as a mammalian protein in claim 1 because said protein possesses regions of variance and to then claim SEQ ID NO:4 as dependent on claim 1 from SEQ ID NO:3.

Claims 1, 3, 6, 30, 31, 32, 35, 38, 49 and 50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated mammalian protein having anti-angiogenic activity, wherein said protein is a receptor for kringle domains 1-4 and/or 5, wherein said protein comprises SEQ ID NO:2 or 3, does not reasonably provide enablement for an isolated mammalian protein having anti-angiogenic activity, wherein said protein is a receptor for kringle domains 1-4 and/or 5, wherein said protein minimally comprises SEQ ID NO:4 or wherein said protein comprises an amino acid sequence having at least 80%, 90% or 95% homology to SEQ ID NO:2, 3 or 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

The instant claims are drawn to proteins having anti-angiogenic activity and which bind to kringle domains 1-4 and/or 5 and which are variants of SEQ ID NO:2, 3 and 4; proteins having anti-angiogenic activity which bind to kringle domains 1-4 and/or 5 and wherein said proteins minimally comprise SEQ ID NO:4.

Troyanovsky et al (Journal of Cell Biology, 2001, Vol. 152, pp. 1247-1254) teach that SEQ ID NO:2 is angiomotin. Troyanovsky et al teach that angiostatin is a proteolytically derived fragment of plasminogen and that said fragments include kringle 1-4 and 5 (page 1247, second column, lines 1-23). Troyanovsky et al teach SEQ ID NO:4 as the clone identified in a yeast two-hybrid screen from proteins which bind to angiostatin (page 1249, legend Figure 2). Troyanovsky et al teach that the only reported signaling pathway that is affected by angiostatin is the induction of Focal Adhesion Kinase activity in vitro and that this activity was induced in

angiomotin transfected cells (page 1251, second column, lines 1-4 under the heading "Angiostatin Induces FAK Activity in Angiomotin-transfected Cells" and page 1252, first column, lines 1-4). Troyanovsky et al teach that the sequence encoding the angiostatin-binding domain of angiomotin was identified and found to comprise proline and alanine rich sequence which included four "PXXP" motifs which are associated with binding sites for Src homology domains found in many signal-transducing molecules (page 1253, first column, lines 3-11). Troyanovsky et al teach that the angiomotin amino acid sequence did not appear to contain any of the signal sequences that are normally found in membrane receptors or secreted proteins (page 1253, first column, bridging sentence to second column). Troyanovsky et al teach that the angiomotin sequence provides little information into exactly how it may be involved in mediating angiostatin inhibition of angiogenesis because the lack of a signal peptide and transmembrane domain indicates that the angiomotin does not act as a typical membrane receptor (page 1254, first column, lines 32-36). Troyanovsky et al teach that the amino-terminus coiled-coil domain as well as the proline rich sequences in the angiostatin-binding domain suggest that angiomotin forms protein complexes. Troyanovsky et al suggest that in consideration of the stimulatory effect of angiomotin on endothelial cell migration which is consistent with an angogenic effect rather than an anti-angiogenic effect, angiostatin actually antagonizes angiomotin function by inhibiting the formation of complexes with other proteins. Thus, it appears from the post-filing date teachings of Troyanovsky et al that angiomotin promotes angiogenesis rather than anti-angiogenesis when bound to "other proteins" , but that angiostatin (derived from the N-terminus of plasminogen) antagonizes the effect of said "other proteins" resulting in an anti-angiogenic effect.

The instant claim are broadly drawn to proteins having at least 80%, 90% or 95% homology to SEQ ID NO:2 or which minimally comprise SEQ ID NO:4, wherein said proteins have anti-angiogenic activity. It appears from the post-filing date art that the structure of SEQ ID NO:2 is not representative of a typical membrane receptor and that SEQ ID NO:2 would exert an angiogenic effect when bound to proteins other than the N-terminus of plasminogen or kringle 1-4 and/or 5.

The instant specification does not disclose the domain of SEQ ID NO:2 responsible for the transmission of the anti-angiogenic signal, nor the binding region of the "other proteins"

which transmit an angiogenic signal. SEQ ID NO:4, although capable of binding to angiostatin would not exert an intracellular signal because it lacks the remainder of SEQ ID NO:2 where the signal transduction would occur. Given the lack of teachings in the specification about the regions of SEQ ID NO:2 responsible for the transmission of the anti-angiogenic signal rather than the angiogenic signal, and the lack of teachings regarding the binding of "other proteins" which would produce the angiogenic signal, one of skill in the art would be subject to undue experimentation in order to make and use the broadly claimed proteins.

Applicant argues in the amendment filed April 8, 2004, that the protein set froth in claim 35 does bind kringle domain 5. This is not in question in the instant rejection because claim 35 specifies that the protein comprises SEQ ID NO:4 which is known to bind to the N-terminal fragment of plasminogen.

Applicant argues that claim 1 has been amended to recite the sequence of SEQ ID NO:4 and thus the full scope of the invention can be made and used without undue experimentation.. This has been considered but not found persuasive. Claim 1 recites sequences having at least 50% homology to SEQ ID NO:4, not SEQ ID NO:4 as alleged in the argument. Further, the specification is not enabling for proteins having antiangiogenic activity wherein said proteins comprise SEQ ID NO:4 for the reason set froth above, i.e. that "SEQ ID NO:4, although capable of binding to angiostatin would not exert an intracellular signal because it lacks the remainder of SEQ ID NO:2 where the signal transduction would occur".

Applicant argues on page 13 of the response that they are merely claiming mammalian proteins wherein the sequence of proteins have the same function with similar sequences and thus only "minor variations" of sequence are encompassed within the claims. This has been considered but not found persuasive. In order to fulfill the requirements of 35 U.S.C. 112, first paragraph, the specification must be enabling for "how to make" the products of the instant claims. The specification does not set forth domains of SEQ ID NO:2 which are important for transmitting the anti-angiogenic signal to other proteins and the post-filing date publication of Troyanovsky et al summarizes the disclosure of SEQ ID NO:2 as "not a typical membrane receptor" and promoting endothelial cell migration which is consistent with an angiogenic effect rather than an anti-angiogenic effect when in the presence of "other proteins" which are not angiostatin. Thus, one of skill in the art would be subject to undue experimentation in order to

make the "minor variants" claimed, which encompass sequences that differ as much as 20% from the instant SEQ ID NO:2 because one of skill in the art would not know what regions of SEQ ID NO:2 are responsible for the transmission of the anti-angiogenic signal versus the angiogenic signal. Further, one of skill in the art would be subject to undue experimentation to make an anti-angiogenic proteins that differ as much as 20% from the instant SEQ ID NO:2 because alterations in the binding region of the "other proteins" could inadvertently cause stranger binding of said other proteins and a concomitant reduction in the antagonistic ability of angiostatin to render an anti-angiogenic signal, given that the identity of the "other proteins" is unknown.

It is again noted that SEQ ID NO:3 encompasses variant sequence due to alternate amino acids at residues 135 and 148-150. Amendment of the above rejected claims to limit the scope to SEQ ID NO:3, and at least 98% sequence homology to SEQ ID NO:2, wherein said proteins exerting an anti-angiogenic activity when bound to the kringle domains 1-4 and/or 5 would overcome this scope rejection.

Claims 7 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 7 is drawn to a peptide capable of binding an N-terminal fragment of plasminogen and which has an amino acid sequence comprising at least 10 contiguous amino acid residues of SEQ ID NO:2. Claim 30 is dependent in part upon the peptides of claim 7. The specification teaches that the subfragment of SEQ ID NO:2 equivalent to SEQ ID NO:4 was isolated in a screening assay designed to isolate proteins which bind to the kringle domains present in the N-terminus of plasminogen, such as angiostatin. SEQ ID NO:4 is 143 amino acids in length. The instant claim 7 encompasses a genus of peptides which minimally comprise 10 contiguous residues of SEQ ID NO:2 and wherein said peptide bind to an N-terminal fragment of plasminogen. The disclosure of SEQ ID NO:4 as binding to angiostatin does not adequately describe the claimed genus. The genus tolerates proteins which minimally comprise regions of

SEQ ID NO:2 rather than SEQ ID NO:4, and further, the genus tolerates proteins wherein said proteins bind to "an" N-terminal fragment of plasminogen which is outside of the kringel domains of plasminogen. For example, members of the genus would include proteins which comprise 10 contiguous residues of SEQ ID NO:2 which bind to residues of plasminogen, but wherein binding of said proteins to plasminogen do not evoke an anti-angiogenic response.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of the peptides which minimally comprise 10 contiguous amino acids of SEQ ID NO:2 and which bind to the N-terminus of plasminogen, per Lilly by structurally describing a representative number of peptides having the characteristics claimed or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the peptides of claim 7 in a manner that satisfies either the Lilly or Enzo standards. The specification provide the complete the complete structure of SEQ ID NO:4 as the only peptide which comprises at least 10 contiguous amino acids of SEQ ID NO:2. The specification does not provide any partial structure of such peptides, nor any physical or chemical characteristics of the peptides nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single peptide of 143 amino acids which fulfills the specific embodiment of claim 7, this does not provide a description of a genus of peptides that would satisfy the standard set out in Enzo.

The specification also fails to describe the peptides of claim 7 by the test set out in Lilly. The specification describes only a single peptide of SEQ ID NO:4. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus." It is noted that SEQ ID NO:4 is 143 amino acids in length and would bind to kringle domains 1-4 and/or 5. However, it is noted that SEQ ID NO:4 would not have anti-antiangiogenic activity as SEQ ID NO:4 would not have an intracellular domain f or signal transduction.

One of skill in the art would reasonable conclude that applicant was not in possession of the claimed genus of peptides.

All other rejections and objections as set forth in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
6/28/2004

Karen A. Canella
KAREN A. CANELLA PH.D
PRIMARY EXAMINER